

Fetal Arrhythmias

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Disclosures

- ▶ Grants support from NIH (RO1HL143485, RO1HL063174) and the Dr. Scholl Foundation
 - ▶ ClinTrials.gov - NCT03775954, NCT03047161
- ▶ **SQUID Fetal Magnetocardiography (fMCG)** has FDA 510K clearance for fetal heart recording
- ▶ **Optically-pumped Magnetometry (OPM)** is investigational for the fetus

Thankyou to the many families who have participated in this research, and the Fetal Care Centers that refer cases for evaluation



- Applied Physics Systems, inc Silicon Valley
- Tristan Technologies, Inc, San Diego

* Qu-Spin, Inc,
Aurora, CO

• SMT, Inc
Rice Lake

• ETS Lindgren, Inc
Wooddale, IL



Dr. Wakai, UW Madison Medical Physics Team

- Device Development
- Arrhythmia and LQTS research

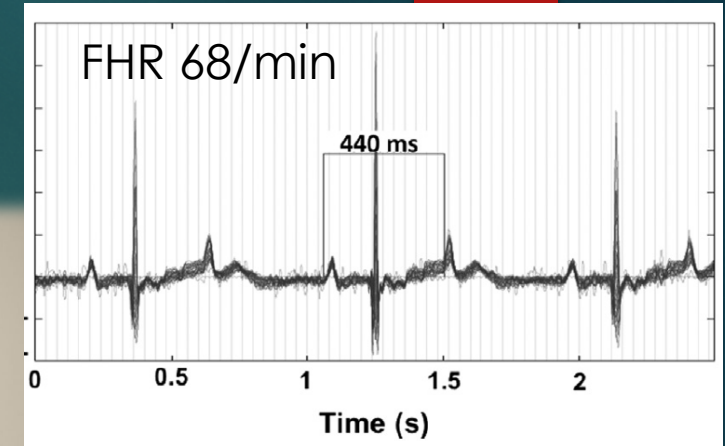
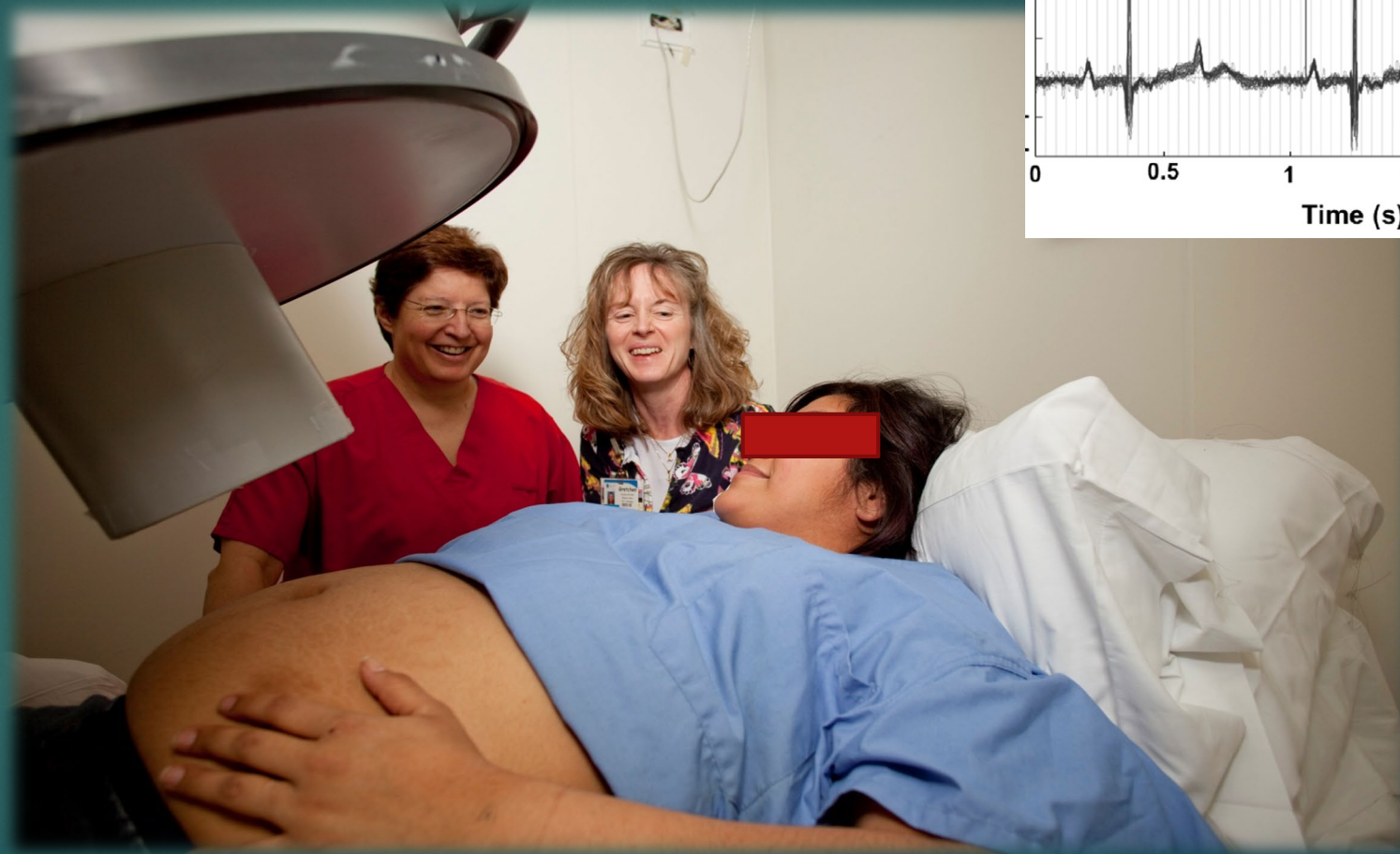


Dr. Strasburger Clinical Team - Herma Heart Institute, Fetal Care Center, and MCW/Marquette Biomedical Engineering
Stillbirth Research and rhythm modeling

Fetal Magnetocardiography (fMCG)

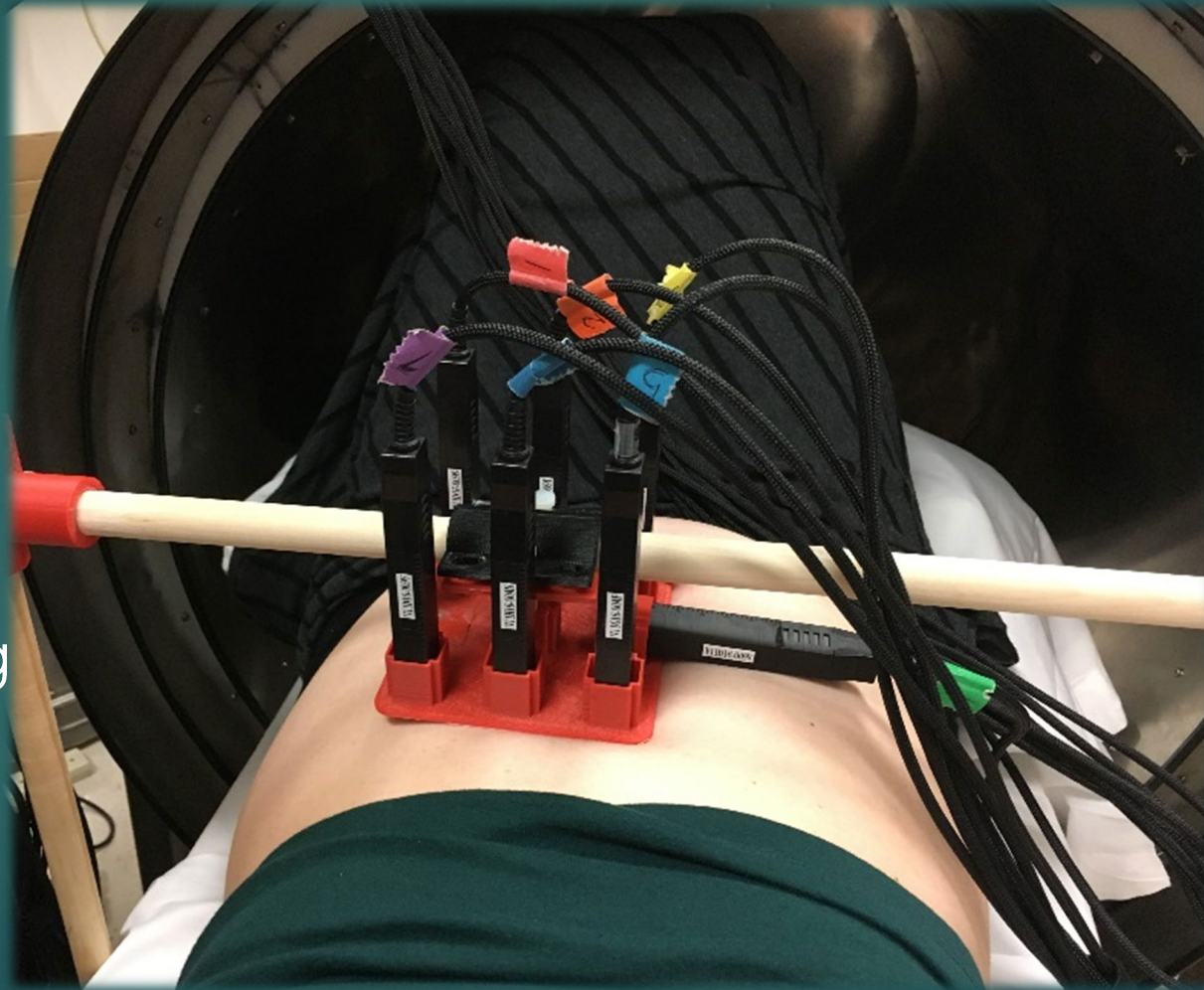
940 pregnant subjects have been evaluated since 1998

- Similar to ECG, not MRI
- Real-time interp
- 15-40 weeks GA
- AHA statement 2014, benefits >> risks
- \$\$\$



Optically-Pumped Magnetometry (OPM)

- 84 pregnant subjects since 2015
- Not FDA approved
 - 1/10th \$ cost
 - New superconducting shielding 10X better



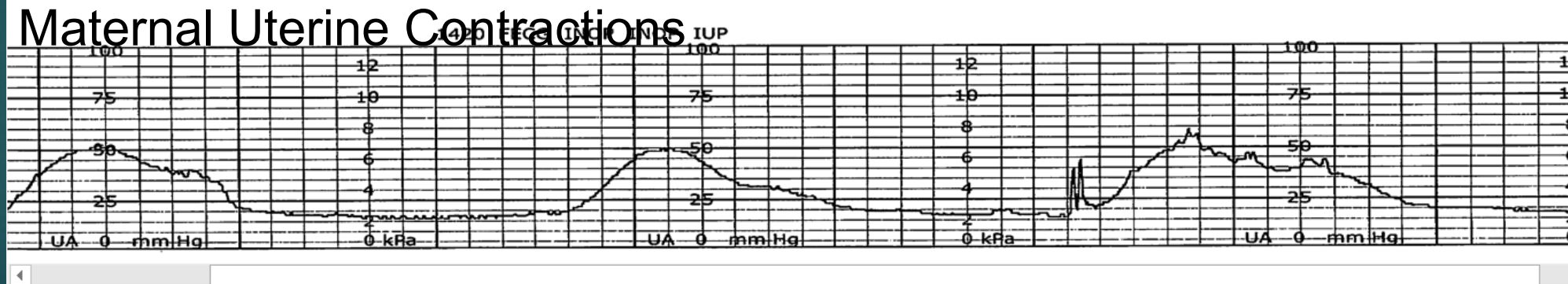
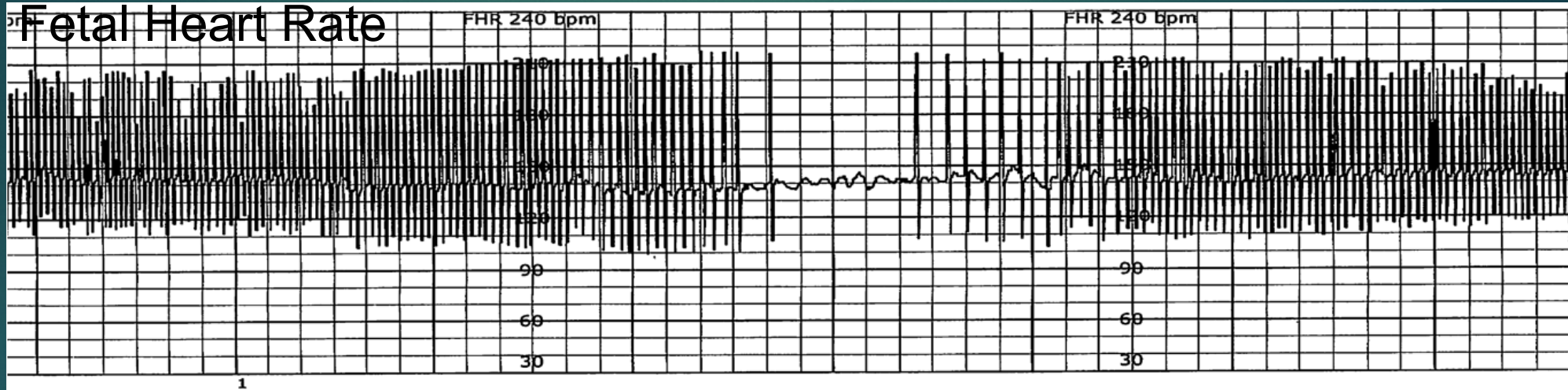
Cardiac Monitoring



- ▶ Heart rate
- ▶ Arrhythmias
- ▶ Hypertrophy and signs of chronic strain
- ▶ STT abnormalities
- ▶ Bundle Branch block
- ▶ WPW, and other conduction disturbances
- ▶ QT prolongation
 - ▶ T wave alternans, J waves, and other repolarization abnormalities
- ▶ Medication changes
- ▶ Serial assessment



Fetal Monitoring during Labor



Overview

- ▶ Tachycardia, bradycardia, and LQTS
 - ▶ Who needs treatment?
 - ▶ Impact of hydrops fetalis (CHF)
- ▶ Antiarrhythmic drugs
 - ▶ Indications, administration, PK, and side effects
- ▶ Current knowledge gaps, and need for additional research

Fetal Arrhythmias

- ▶ Usually 2nd and 3rd trimester
- ▶ 1-2% of all pregnancies, mostly benign ectopic beats
 - ▶ 10-15% are life-threatening (SVT, Atrial flutter, JET, VT, Torsades de Pointes, Congenital AV block)
- ▶ Risk factors
 - ▶ Familial inheritance
 - ▶ High risk pregnancies
 - ▶ Nutritional deficiency – Vit D, Mag, Ca, K
 - ▶ Maternal medications
 - ▶ 87% of our subjects were taking medications other than PNV
 - ▶ 45% were taking at least one QTc-lengthening drug, and 18% were taking 2 or more. Half were for fetal indications.

Unique Aspects of Fetal Treatment with Antiarrhythmic Drugs

- ▶ Fetal arrhythmia therapy is one of the oldest fetal interventions, and one of the most successful, but it is “Off-Label”
- ▶ Treatments impact the entire maternal-fetal-placental triad
- ▶ High AA drug doses needed to achieve success
- ▶ Paucity of means of assessing drug levels for fetus
- ▶ Maternal drug levels - slow turn-around, limited availability

Unique Aspects of Fetal Treatment with Antiarrhythmic Drugs

- ▶ Over 200 drugs on the market increase the QTc interval
 - ▶ Ondansetron, oxytocin, antidepressants, ADHD meds, opioids, etc
- ▶ Delay in onset - 5 half-lives to see full effect
- ▶ TP transfer influenced by GI absorption, molecular size, protein binding, ionization, by gestation, etc
- ▶ Fetal intravascular access has high mortality
 - ▶ Intramuscular absorption is good, but risk of sciatic injury

Fetal Tachycardia

- ▶ ~1:2500 pregnancies
- ▶ Mortality 40-60% without treatment, 0-7% with treatment, unless hydrops, then 10-20%
- ▶ Treat if sustained, GA<36 wks, and/or FHR>200/min
 - ▶ VT, JET, treat even if rate <200/min



Differences in treatment success between SVT and flutter and between SVT with and without hydrops

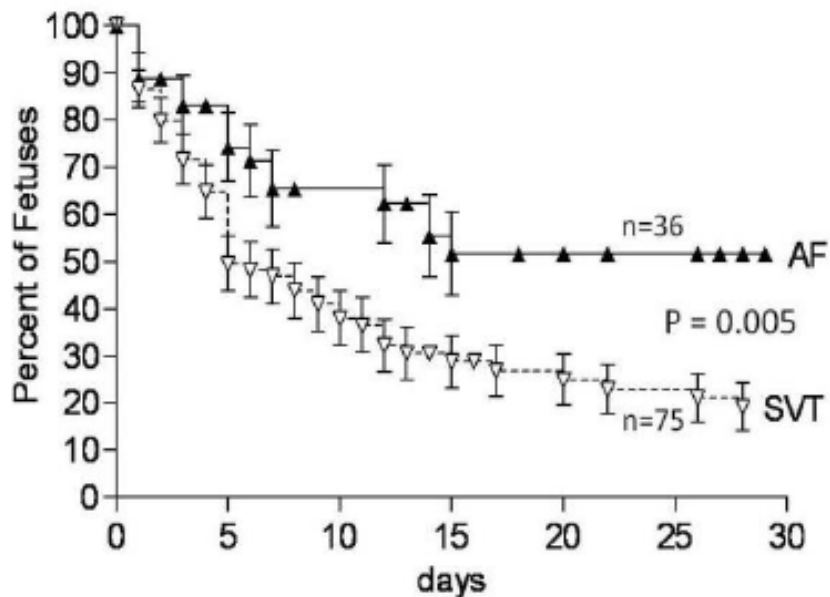


Fig. 1. Freedom from termination of fetal SVT vs. AF despite drug treatment (n=111). AF responded more slowly to drug therapy than SVT (HR=2; p=0.005). Cardioversion at 5 and 10 days was achieved in 50% and 63% of fetuses with SVT and in 25% and 41% of cases with AF.

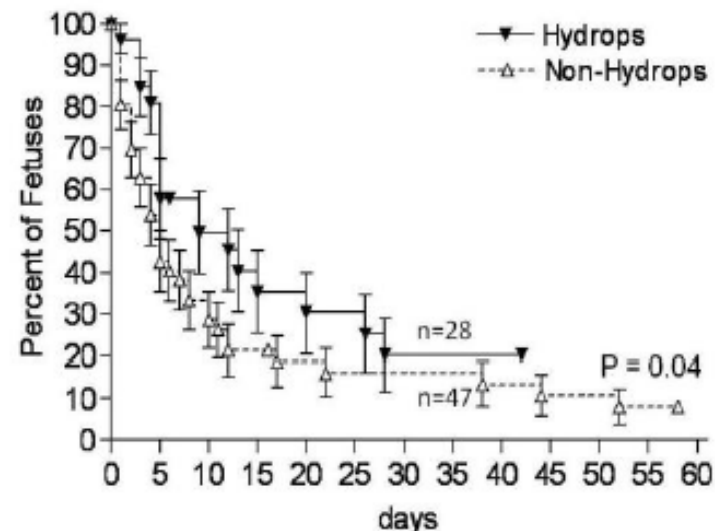


Fig. 2. Freedom from termination of fetal SVT with and without hydrops (n=75). Treatment failure was also more likely if SVT was associated with fetal hydrops (HR=1.8; p=0.04) at the time of diagnosis. It took more than twice as long (9 vs. 4 days) for conversion of 50% of SVT cases to a normal rhythm if fetuses were hydropic. 21% of the hydropic cases died.

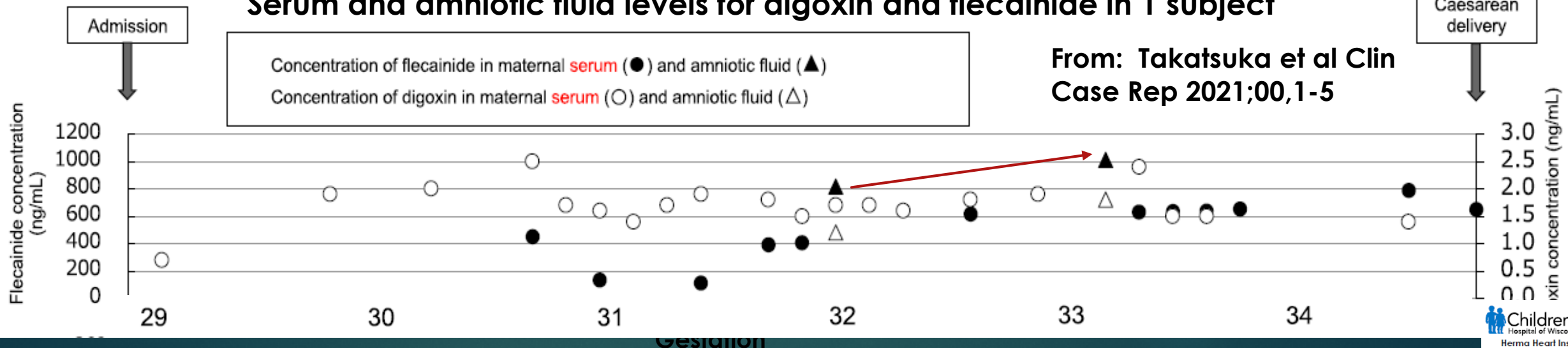
Transplacental Drugs for SVT and A Flutter

AA Agent	F:M drug ratio Route	Efficacy acute and chronic	Intraamniotic accumulation	Side Effects
<u>Digoxin</u> NaK ATPase Inhib Class C	0.8:1, ↓'d if hydrops, PO, IV, fetal IM/IC	50-60%, combined with other AA 80%	Higher, not reflected in [fetal]	N/V, arrhythmias
<u>Flecainide</u> Na Chan Inhib Class C	1:1(+) PO	60%	27X serum level	CNS, brady, ↑QTc
<u>Sotalol</u> K chan Inhib/B blocker Class B	0.9:1(+) PO	50-60%	1.6-28X serum level	CNS, brady, ↑QTc
<u>Amiodarone</u> Multi-chan Inhib Class D	0.4:1, long T ½ after PO loading; Rare intracordal or peritoneal admin	90+%	Lipophylic, All tissues	Brady; M/F hypothyroidism, ↑QTc, breast feeding CI
(Adenosine)	NOT Recommended, Dir intracordal admin	LOW	0	Short-acting

Intra-amniotic Drug Accumulation

- ▶ Antiarrhythmic agents with intra-amniotic accumulation
 - ▶ Sotalol 28 :1 [amniotic fluid]/[mat serum]
 - ▶ Flecainide 1.6 – 27:1
- ▶ Cuneo et al UOBGyn 2021:57:342-48
 - ▶ Reduction in dose using home hand-held Doppler for detection of recurrence
 - ▶ Postnatal <40% recurred

Serum and amniotic fluid levels for digoxin and flecainide in 1 subject



Fetal AV block

- ▶ ~1:10,000 pregnancies
 - ▶ Isoimmune SSA-mediated
 - ▶ 1-2% of women with lupus, 16% recurrence risk (7.5% after early HCQ)
 - ▶ SSA negative with structurally normal heart (LQTS)
 - ▶ CHD – AV septum
- ▶ Prognosis dependent on etiology



Transplacental Tx for AV Block

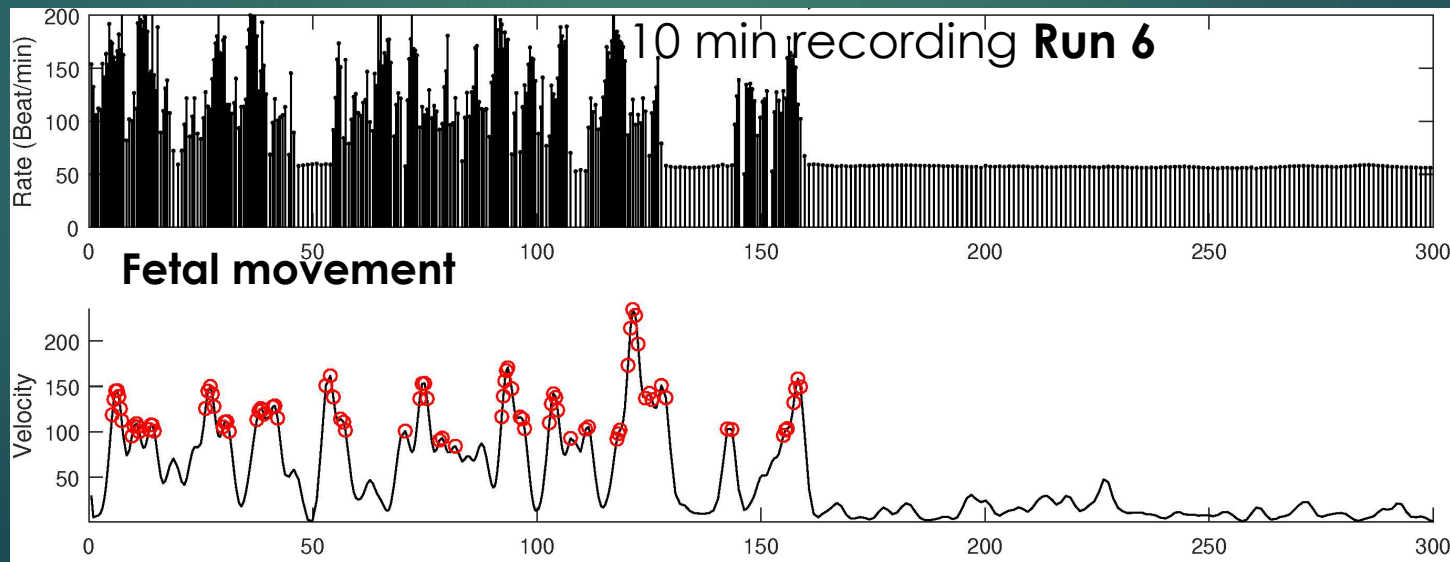
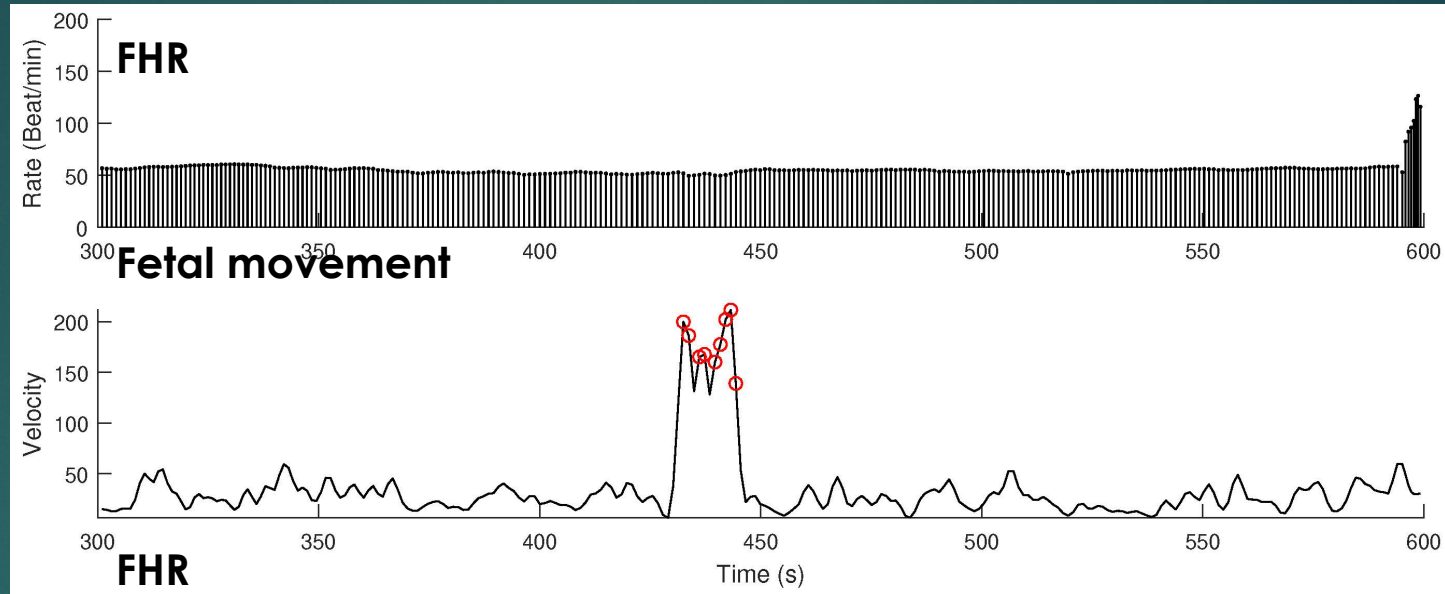
Drug	Indication/durationRoute	F:M drug ratio	Efficacy acute and chronic	Side Effects
<u>Dexamethasone</u> Fluorinated glucocorticoid	PR on echo > 170 ms or AV block onset PO	0.5 F:M, ↓Mab levels	20-40% reversal of 2:1 block, May ↓postnatal cardiomyopathy	Mat HTN, ↑ glu, wt gain, osteopor, etc. Trf breast milk
<u>IVIg</u> Anti-inflammatory, Blocks F2/FAB receptors in placenta	Hydrops IV	0.5-1.0:1	in HF, ↓'d mortality from 80-25% \$\$\$ - preapproval needed	Allergic Rxn, Vaccines
<u>Hydroxychloroquine</u> TLR blocker, ↓ Endosomal pH	Prior infant with NLE PO	1.04:1	↓'d Heart Block risk from 16 to 7%	↑QTc
<u>Terbutaline</u> Beta Agonist	FHR<50/min, if CHD <55/min PO	1-1.5:1	↑ FHR by 5-10 beats/min, Not proven to ↑ survival	↑ mat HR, arrhy ^{''} CNS

Long QT Syndrome (Inherited Arrhythmias)

- ▶ 1:2000
- ▶ Very underrecognized, since 40% or more of cases are de novo (fetus as proband)
- ▶ Unexplained stillbirth (3-8%)
- ▶ 5-10% of SIDS
- ▶ Sinus brady, AV block, and Torsades de Pointes (TdP)



FMCG Visit 1, Mat LQTS 2: 29 6/7 wks GA



FMCG Mat LQTS2, Visit 1: 29 6/7 wks GA



Torsades de Pointes in the Fetus

- ▶ 7/9 were not recognized by fetal echocardiography
- ▶ TdP can appear slow, mimicking sinus rhythm
- ▶ Hydrops
- ▶ De novo LQTS accounts for majority, 45% mortality
- ▶ Familial LQT2 or 3 or rare variants
 - ▶ No mortality with treatment



Transplacental Drugs for VT and TdP

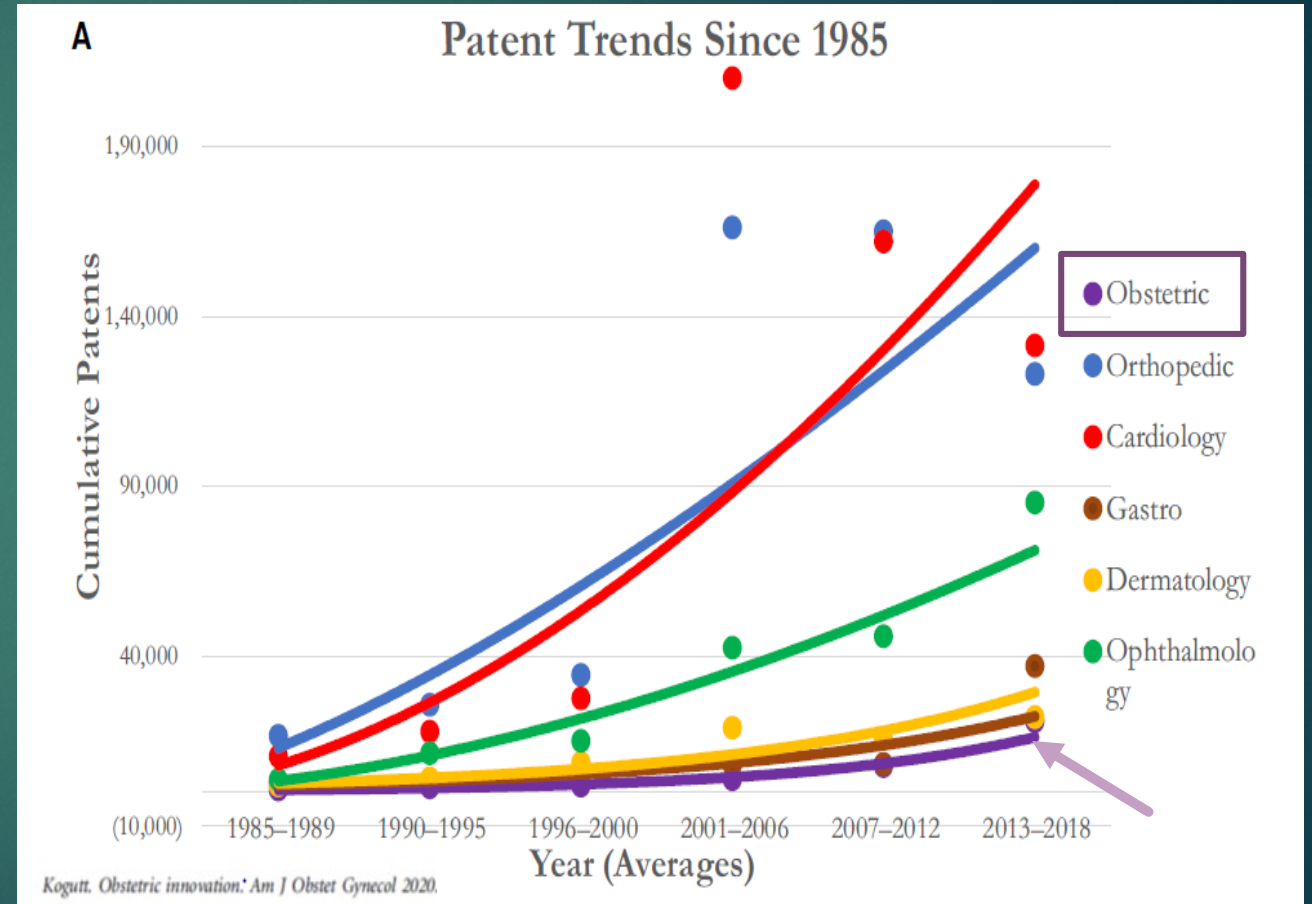
AA Agent	F:M drug ratio	Efficacy acute and chronic	Intraamniotic accumulation	Side Effects
<u>Magnesium Sulfate</u> Class	1:1(+) IV, PO Co-admin Vit D	80+%,	Baseline high	CNS
<u>Propranolol, Other BB</u> Class C	0.25:1 IV, PO	Partial, ↓QTc, lowers Vfibr risk	2-4X	Brady, Nadolol concentrates in breast milk
<u>Lidocaine/Mexiletine</u> Na ch Inhib	0.5:1 IV/PO	50+%	0.5-1.0	CNS, Paradox ↑QTc
Drugs to treat VT with NI QTc, Not Torsades de Pointes				
<u>Flecainide</u> Na Inhib Class C	1:1	60%	27X serum level	CNS, brady, ↑QTc
<u>Sotalol</u> K Inhib/B bl. Class B	0.9:1(+)	50-60%	28X serum level	CNS, brady, ↑QTc
<u>Amiodarone</u> Class D	0.4:1, long-term after loading	90+%	All tissues	Brady, no breast feeding

Knowledge Gaps and Research Barriers

- ▶ Fetal cardiac monitoring and drug monitoring
- ▶ Education
- ▶ Research Recruitment
 - ▶ Limited enrollment of non-English speaking subjects and minors
 - ▶ Complicated site set up
- ▶ Access to postnatal follow up records arduous
 - ▶ Institution-specific release-of-information forms
 - ▶ Costs, delays
 - ▶ Separation of ECG's from the EMR
- ▶ Other Barriers: Institutions unwilling to take on costs and Industry partners unwilling to take on the risk

Suggestions for Improving Fetal Drug and Device Research Translation

- ▶ Federally-funded Consortium for Fetal Drugs and Devices (modelled after the FDA Pediatric Device Consortium)
- ▶ Prospective data registry for antiarrhythmic agents in pregnancy
- ▶ Prospective international collaborative clinical trials



Kogutt et al JOBGyn 2020

Thank you



Door County Visitor Bureau